Armed Forces College of Medicine

AFCM

Treatment of Hypertension

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INTENDED LEARNING OBJECTIVES (ILO)

Lecture 1:

1) Classify the groups of antihypertensive drugs according to their mechanisms of action
2) Identify the role of diuretics in the treatment of hypertension
3) Explain the role of beta –blockers as antihypertensive drugs
4) Explain the adverse effects and drug interactions of Beta-blockers as antihypertensive drugs

- **Hypertension is the most common cardiovascular disease.**

- **Sustained arterial hypertension damages blood vessels in kidney, heart, and brain and leads to an increased incidence of renal failure, coronary disease, heart failure, stroke, and dementia.**

- **Effective pharmacologic lowering of blood pressure has been shown to prevent damage to blood vessels and to substantially reduce morbidity and mortality rates.**

- **However, unfortunately, not all patients with hypertension will have adequate blood pressure control.**

Hypertension

Systemic Hypertension: Defined as persistent elevation of blood pressure to above 140/90 mmHg in at least 3 measurements on at least 3 separate occasions.

Cause: Hypertension results from increased peripheral vascular arteriolar smooth muscle tone.

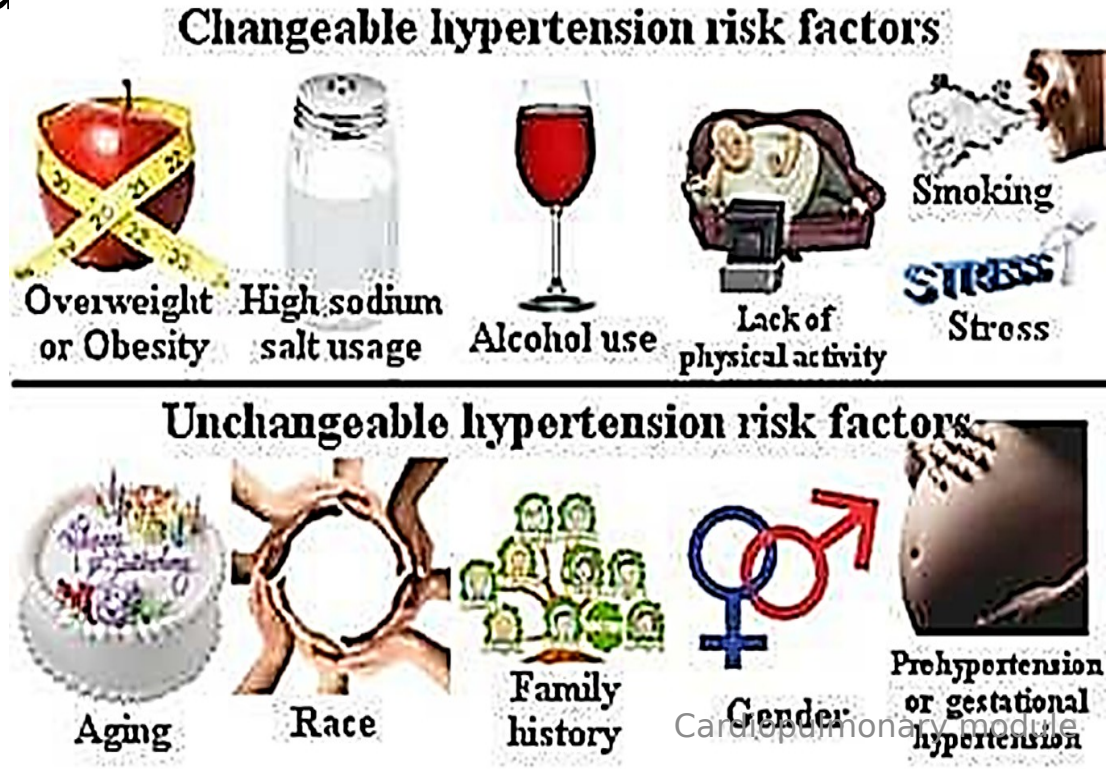
Other positive risk factors include smoking; metabolic syndrome, including obesity, dyslipidemia, and diabetes; manifestations of end-organ damage at the time of diagnosis; and a family history of cardiovascular Disease

- **Pre-hypertension:** Recently, blood pressure from 120/80 mmHg to 139/89 mmHg is defined as prehypertension. It identifies individuals at high risk of developing hypertension.

Types

1-Primary (Idiopathic, Essential): 90 - 95%

Of Unknown cause, but has many risk factors



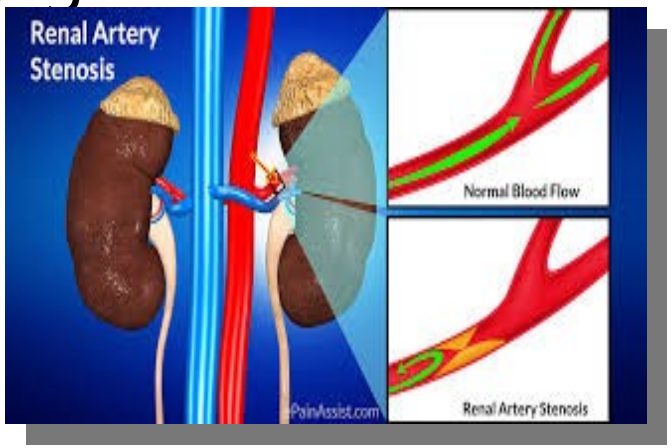
Atherosclerosis

&

Diabetes Mellitus

Types

2-Secondary: 5 - 10% Of known cause e.g.:

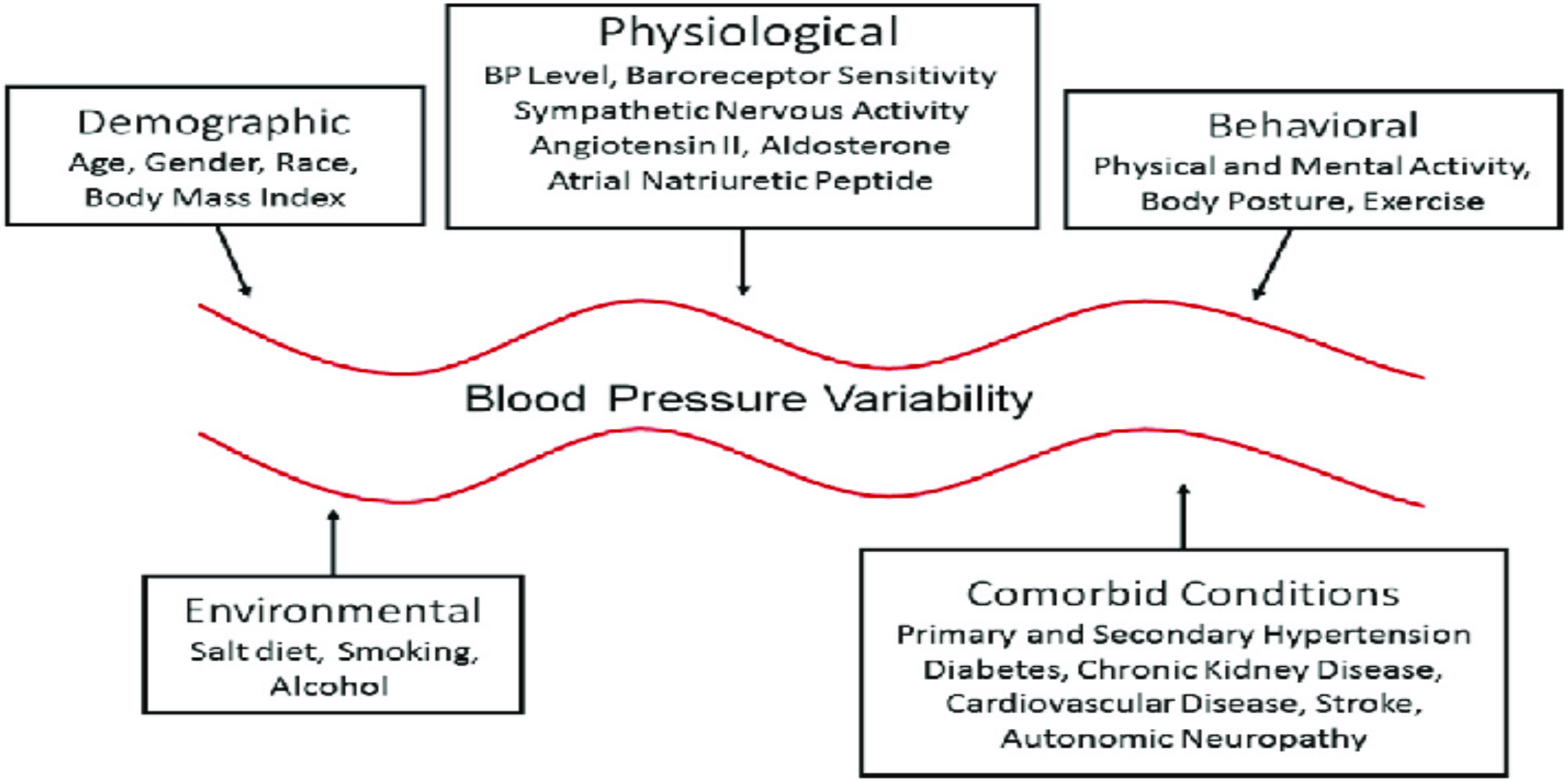


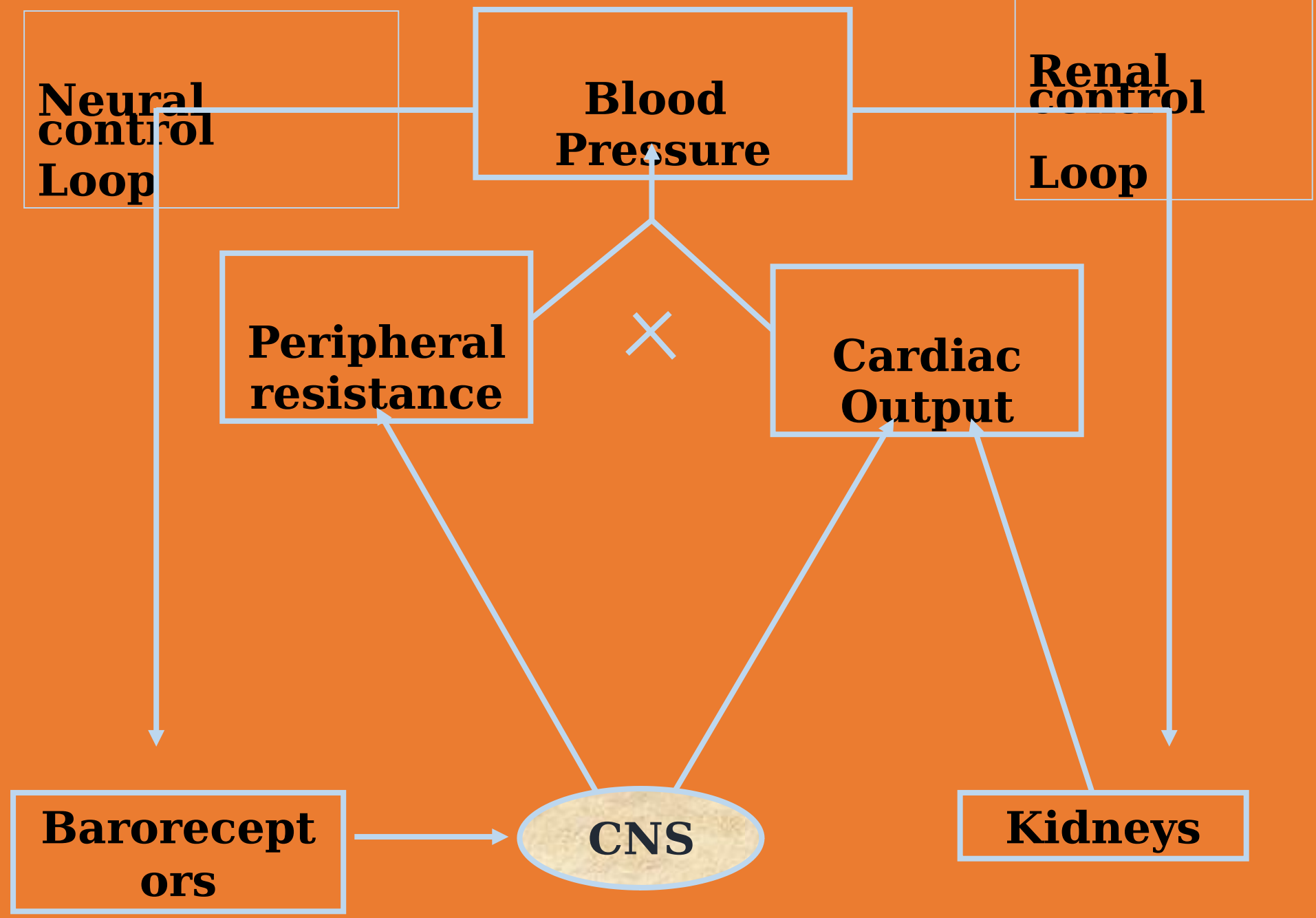
Diseases e.g.

- Renal parenchymatous diseases
- Renal artery stenosis
- Coarctation of the aorta,
- pheochromocytoma,
- Cushing's disease, and
- primary aldosteronism

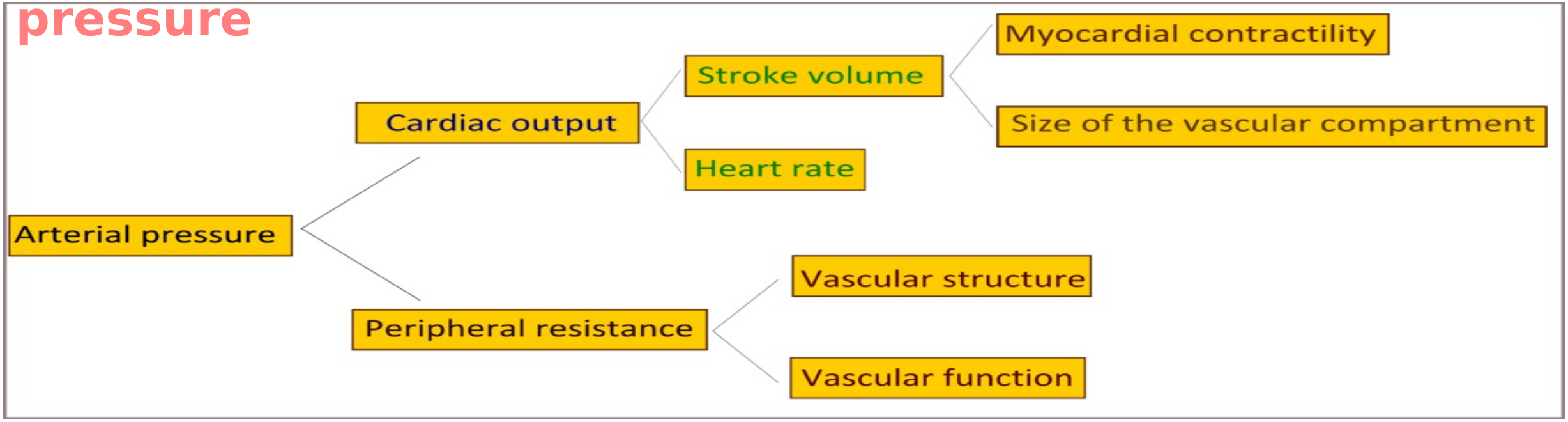
Drugs e.g. Corticosteroids, Contraceptives,
Clonidine withdrawal
& Cheese reaction with MAOI.

Some of them are amenable to definitive


Physiological
BP Level, Baroreceptor Sensitivity
Sympathetic Nervous Activity
Angiotensin II, Aldosterone
Atrial Natriuretic Peptide
Demographic
Age, Gender, Race,
Body Mass Index
Behavioral
Physical and Mental Activity,
Body Posture, Exercise
Blood Pressure Variability
Environmental
Salt diet, Smoking,
Alcohol
Comorbid Conditions
Primary and Secondary Hypertension
Diabetes, Chronic Kidney Disease,
Cardiovascular Disease, Stroke,
Autonomic Neuropathy

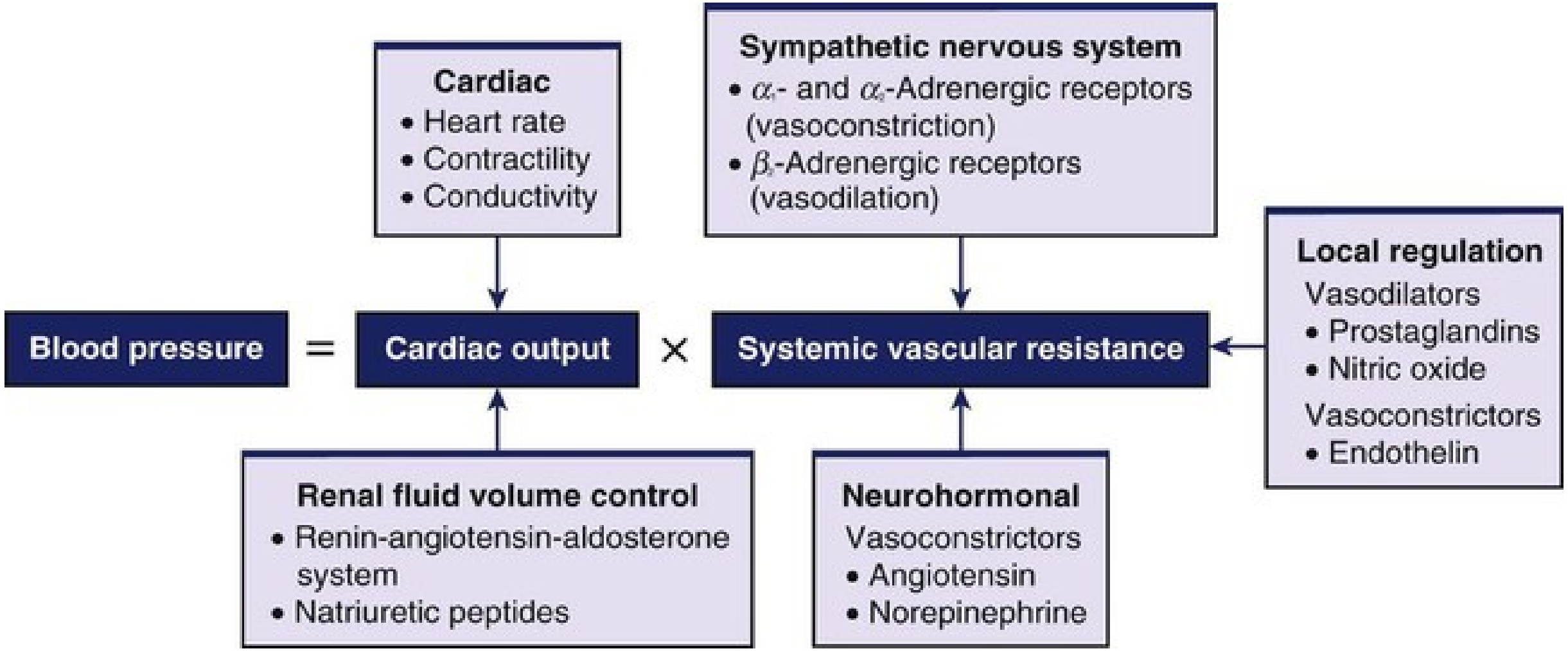

Neural control Loop
Blood Pressure
Renal control Loop
Peripheral resistance
X
Cardiac Output
Baroreceptors
CNS
Kidneys

factors influencing arterial blood pressure



- Baroreflexes, mediated by autonomic nerves, act in combination with humoral mechanisms, including the renin-angiotensin-aldosterone system, to coordinate function and to maintain normal blood pressure.
- Finally, local release of vasoactive substances from vascular endothelium may also be involved in the regulation of vascular resistance. For example, endothelin-1 constricts, and nitric oxide dilates blood vessels.

In hypertensive patients the baroreceptors and the renal blood volume-pressure control systems appear to be "set" at a higher level of blood pressure



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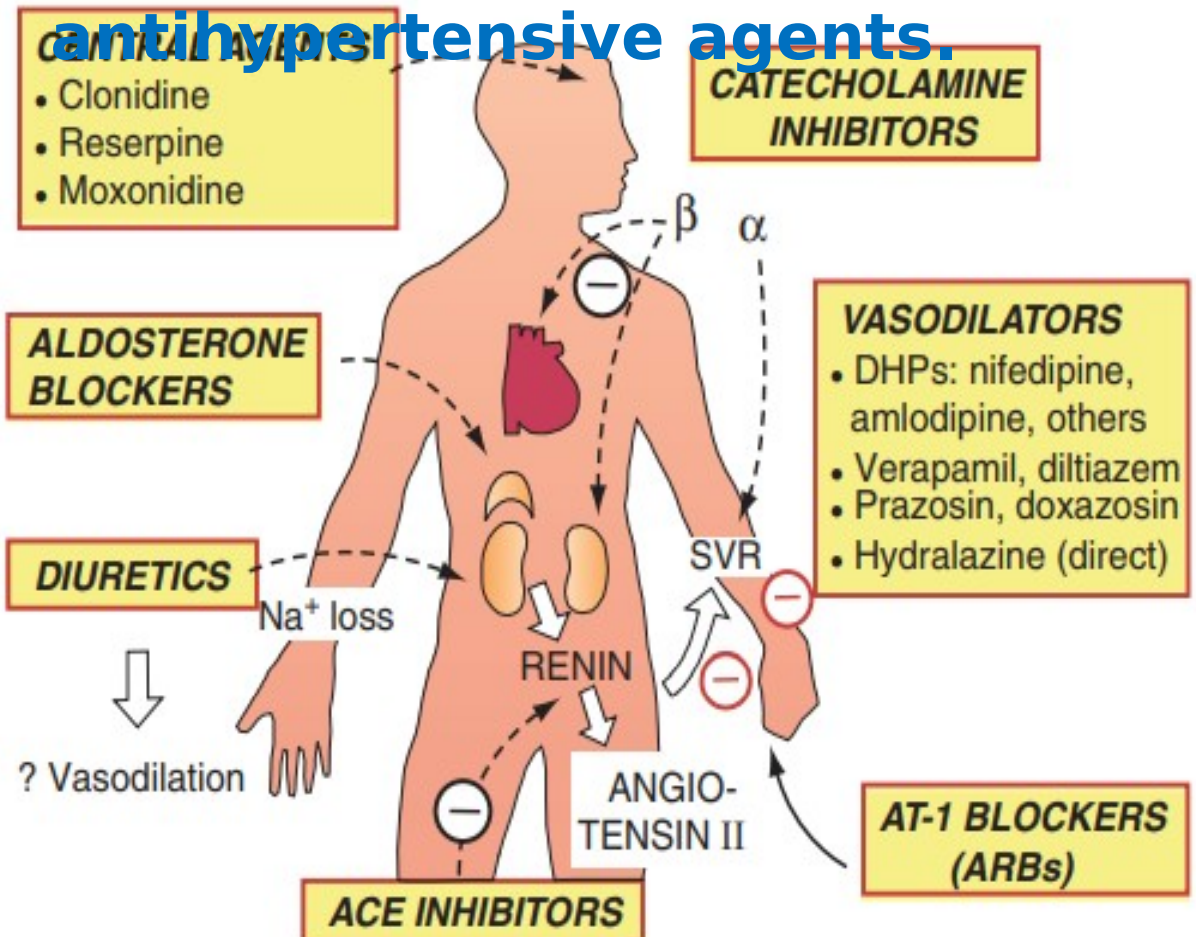
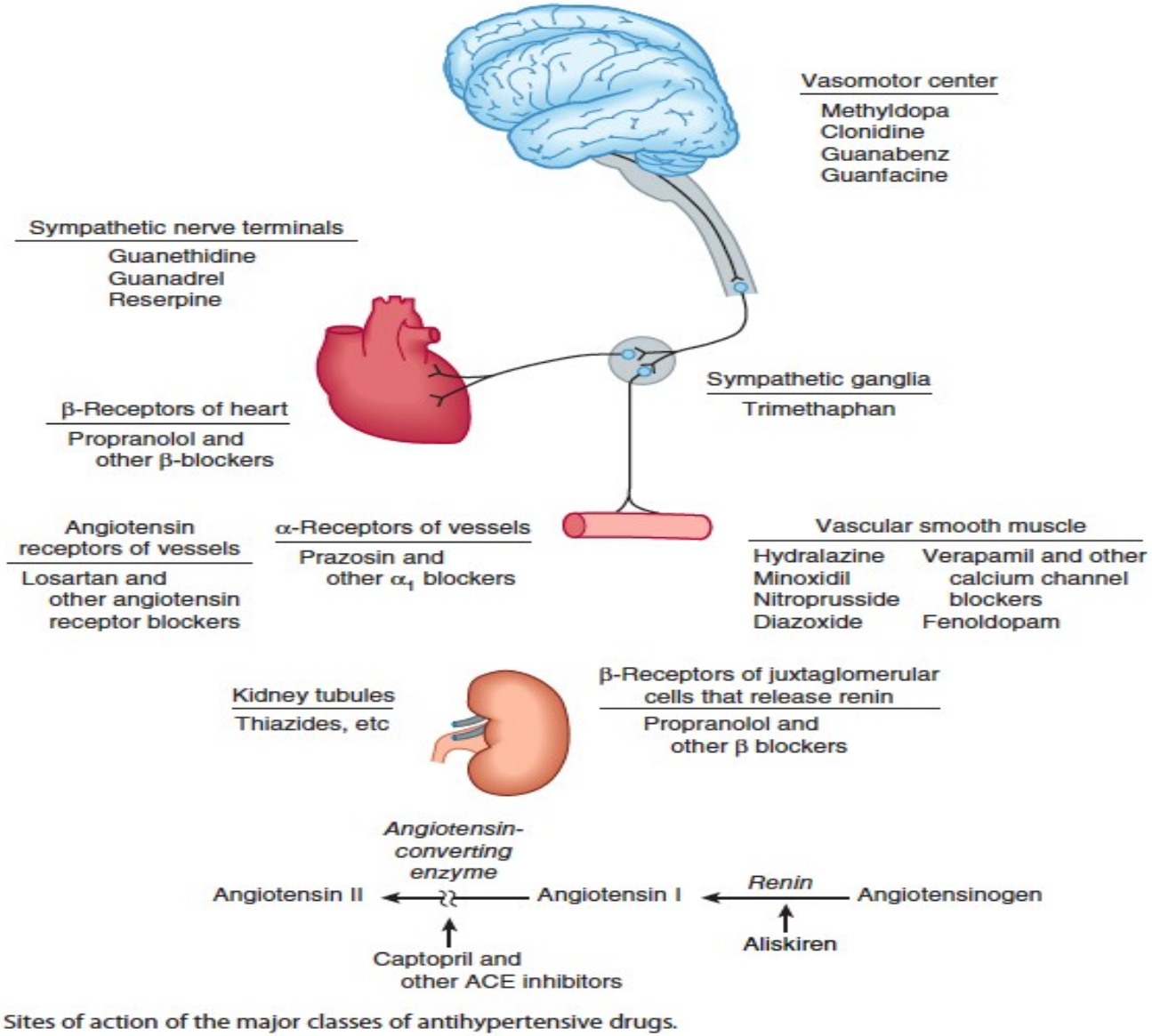
Classification of Antihypertensive Drugs

Sites of action for antihypertensive agents.





Sites of action of the major classes of antihypertensive drugs.

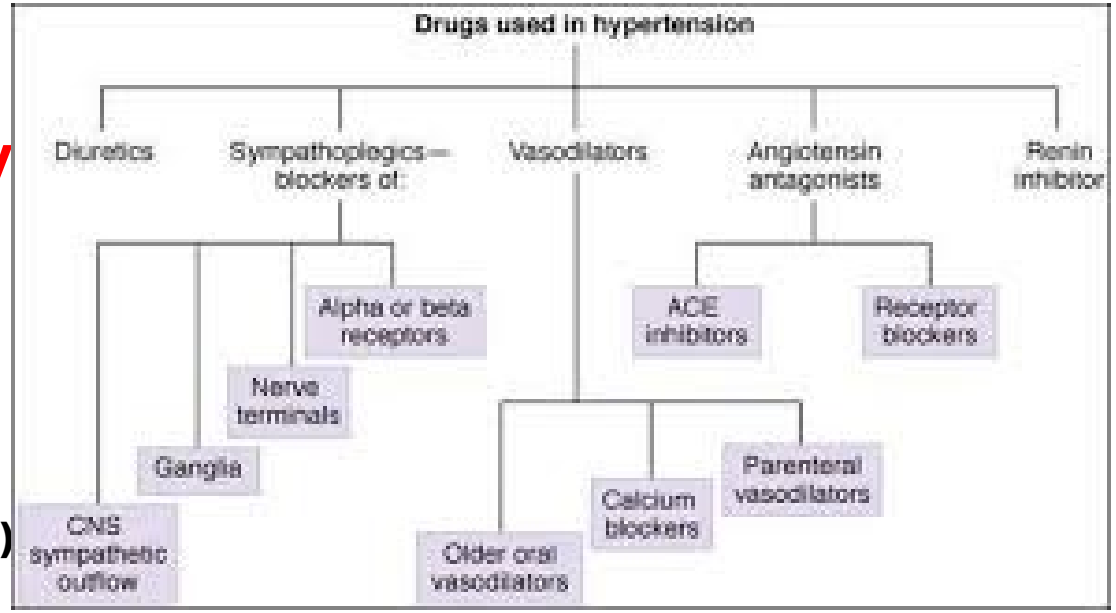
Because hypertension is frequently multifactorial in origin, it may be difficult to find the ideal drug for a given patient and drug combinations are often used at low to moderate doses, which often produce better blood pressure lowering than a single agent at a maximum dose.

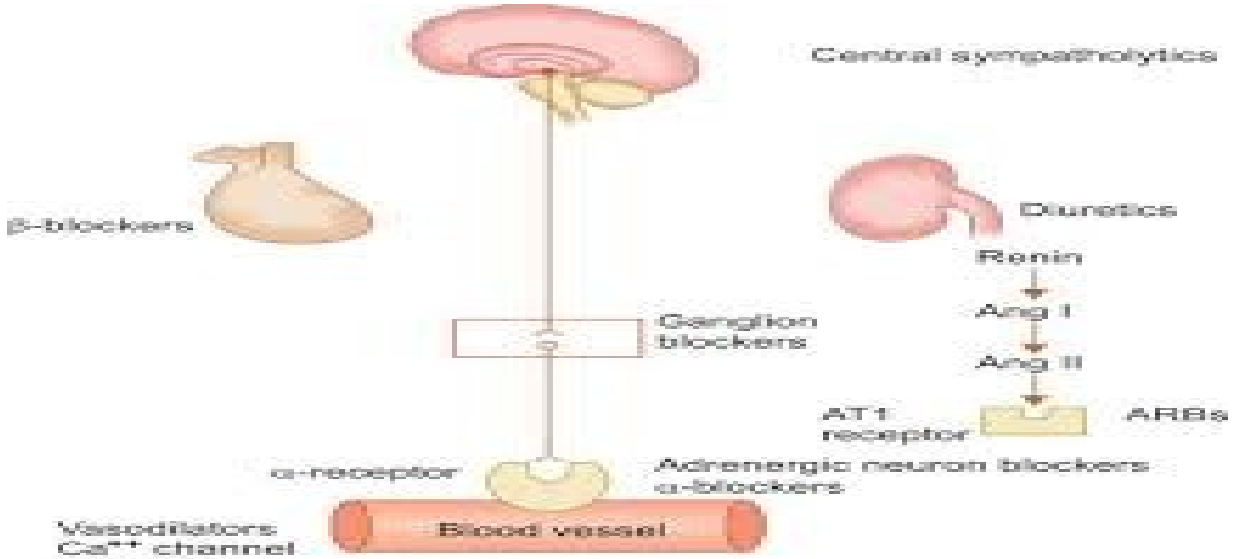
Neal L Benowitz, MD. In: Katzung BG (ed.): (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

The goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality.

Medication classes for treatment of hy

- Diuretics.
  1. thiazides for mild to moderate
  2. loop for severe and renal patients
- Calcium Channel Blockers.
  1. Dihydropyridine
  2. Non-dihydropyridine
- Angiotensin Converting Enzyme Inhibitors (ACEIs)
- Angiotensin II Receptor blocker (ARBs).
- Mineralocorticoid receptor antagonists
- Beta Blockers.
  1. Nonselective
  2. Cardio selective
  3. With vasodilating properties
- Centrally acting α2-agonists
- α1 adrenoreceptor antagonists
- Direct Vasodilators.
- Direct renin inhibitors-
  1. Decrease release
  2. Renin receptor blocker





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Managemen

1-Definitive diagnosis.

2-If 2ry type: treat the cause.

3-Lifestyle modifications: for all patients , but not adequate alone except in case of prehypertension.

a) 1- Weight reduction

b) 2- Diet rich in **fruits, vegetables, and low-fat dairy products** with a reduced content of saturated and total fat **8 -14 mmHg**

c) 3- **Dietary sodium restriction**: reduce daily dietary sodium intake to less than or equal to 100 mEq (2.4 g sodium or 6 g sodium chloride) **2 - 8 mmHg** With the advent of diuretics, sodium restriction was thought to be less important

4- Drugs.

I- Diuretics

Mechanism of Antihypertensive Action of Diuretics:

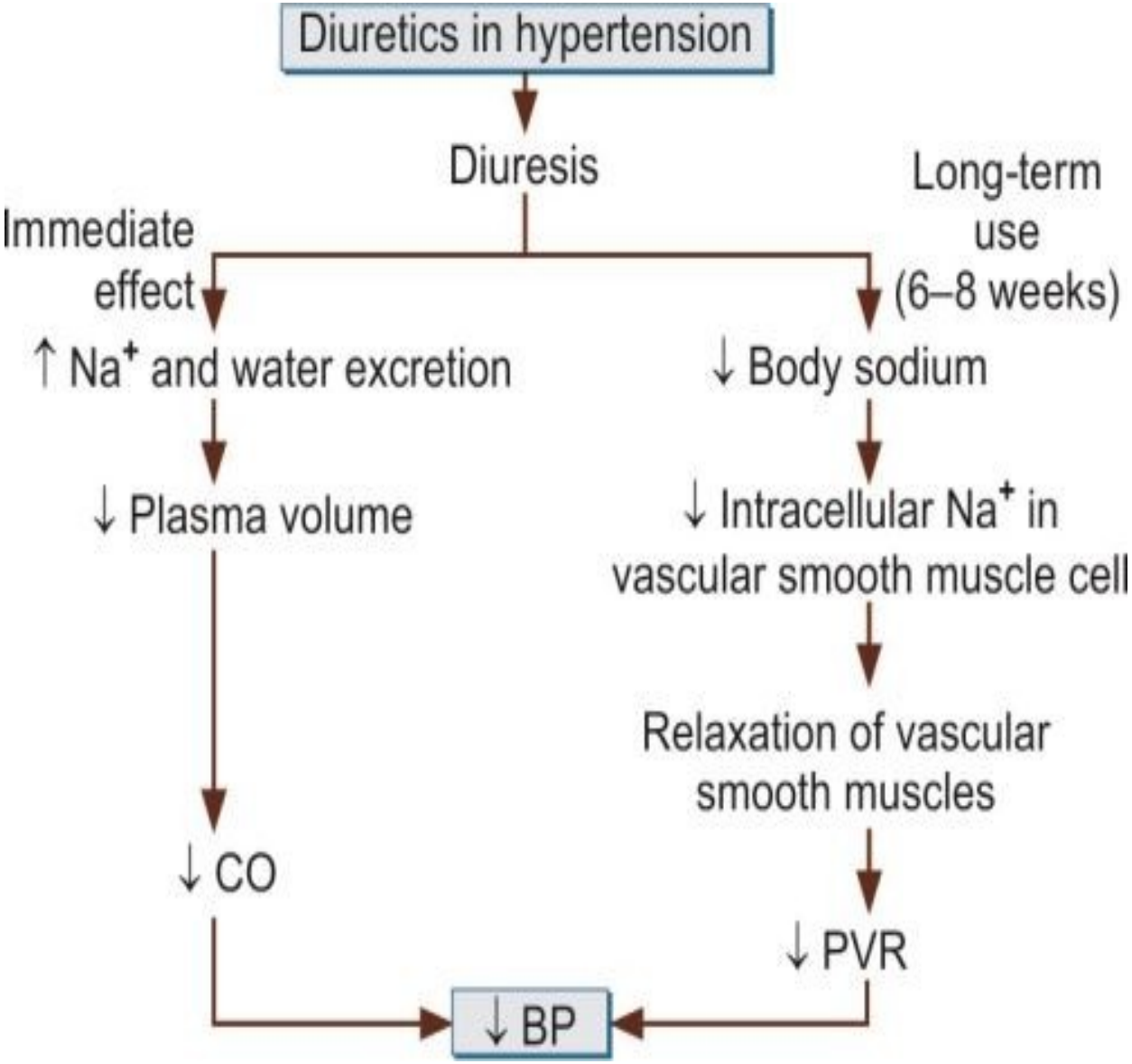
1- Diuretic Action → decrease Blood Volume → decrease Cardiac output → decrease Blood pressure (discussed later)

2- Thiazide diuretics in addition have a **direct vasodilator action** by:
a- Deplete Na+ from the arterial wall.
b- Open K + channels → Hyperpolarization.
c- Release of vaso-dilator Prostaglandins (PGs).

3- Indapamide: (A thiazide analogue) When used in a small

1. DIURETICS

- Diuretics lower blood pressure primarily by depleting body sodium stores.
- Initially, diuretics reduce blood pressure by reducing blood volume and cardiac output.
- After 6–8 weeks, cardiac output returns toward normal while peripheral vascular resistance decreases.
- Diuretics can be used as first-line drug therapy for hypertension and can reduce by 10–15 mm Hg in most patients.
- Low-dose diuretic therapy is safe, inexpensive.
- In more severe hypertension,



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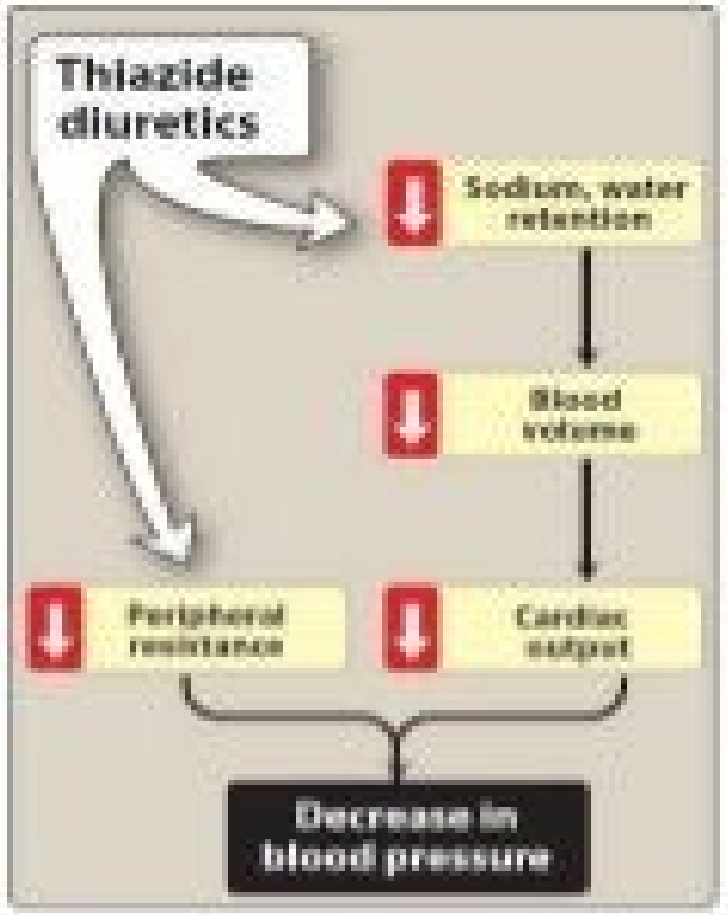
A. Thiazide diuretics

- *Hydrochlorothiazide and Chlorthalidone*
- Thiazide diuretics are appropriate for most patients with mild or moderate hypertension and normal renal and cardiac function.
- With the exception of ***metolazone,*** *thiazide diuretics are not effective in patients with inadequate* kidney function (creatinine clearance, less than 50 mL/min).
- Excessive use of any diuretic is dangerous in patients with hepatic cirrhosis, borderline renal failure, or heart failure.
- Loop diuretics may be required in these patients.



B. Loop diuretics

- *Furosemide, bumetanide, and torsemide*
- Used in
  - severe hypertension, when multiple drugs with sodium-retaining properties are used;
  - in renal insufficiency, when glomerular filtration rate is less than 30–40 mL/min; and
  - in cardiac failure or cirrhosis, in which sodium retention is marked.
- They cause decreased renal vascular resistance and increased renal flow flow via prostaglandin actions on kidney vasculature. (*Loop diuretics have also been shown to induce expression of the cyclooxygenase COX-2, which participates in the synthesis of prostaglandins from arachidonic acid).*

C. Potassium-sparing diuretics.

- *Amiloride and triamterene*
- *Spironolactone and eplerenone* (aldosterone-receptor antagonists)

  Reduce potassium loss in the urine.

- *Spironolactone has the additional benefit of diminishing* the cardiac remodeling that occurs in heart failure.
- Potassium-sparing diuretics may produce hyperkalemia, particularly in patients with renal insufficiency and those taking

Use of Diuretics In hypertension:

1- Thiazides:

In Mild and Moderate hypertension and normal renal and cardiac function.

2- Loop diuretics:

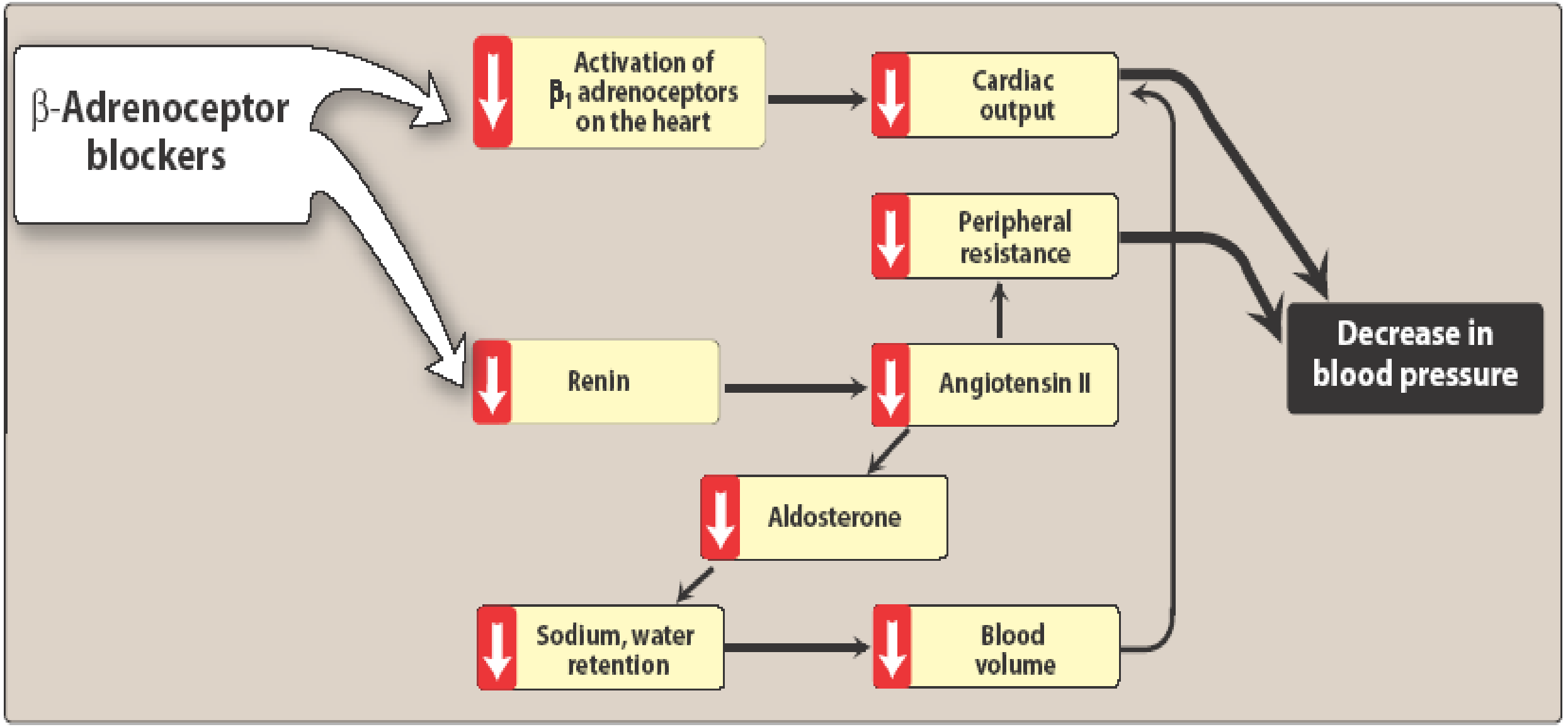
a- Severe hypertension.
b- Hypertensive emergencies.
c- Hypertension with renal insufficiency.
d- in cardiac failure or cirrhosis.

3- Potassium retaining diuretics:

a- In combination with other diuretics to correct hypokalemia.
b- Some cases of resistant hypertension

2. β-ADRENOCEPTOR–BLOCKING AGENTS

- **Actions:** The β-blockers reduce blood pressure primarily by
  - **Decreasing cardiac output: main mechanism**
  - **↓ sympathetic outflow**
  - **By acting on peripheral presynaptic β adrenoceptors to reduce sympathetic vasoconstrictor nerve activity**
  - **↓ renin**
  - **↓ angiotensin II**
  - **↓ aldosterone**



Actions of β–adrenoceptor blocking agents.

Examples:

1. *Metoprolol and atenolol*.
   - Selective blockers of B_1 receptors
   - Most commonly used
2. The nonselective β-blockers, such as *propranolol* and *nadolol, are contraindicated* → block β_2 → bronchial asthma.
3. Non-selective beta blockers have now been largely replaced by cardioselective β blockers such as metoprolol and atenolol.
4. All β-adrenoceptor-blocking agents are useful for lowering blood pressure in mild to moderate hypertension.
5. In severe hypertension, β blockers are especially useful in preventing the reflex tachycardia that often results from treatment with direct vasodilators.

Adverse effects

1. **Common effects:**
   - Bradycardia, fatigue, lethargy, hallucinations, hypotension, sexual dysfunction
2. **Alterations in serum lipid patterns:**
   - May disturb lipid metabolism, decreasing high-density lipoprotein cholesterol and increasing plasma triglycerides.
3. **Drug withdrawal:**
   - The dose of these drugs must be tapered over 2 to 3 weeks in patients with hypertension and ischemic heart disease.

β-ADRENOCEPTOR–BLOCKING AGENTS with vasodilating properties

- **Labetalol, Carvedilol block α1, beta1, and beta2 receptors** so they have both β-blocking and vasodilating effects.
- Blood pressure is lowered by reduction of systemic vascular resistance (**via α blockade)** without significant alteration in heart rate or cardiac output.
- Because of its combined α- and β-blocking activity, labetalol is useful in treating the hypertension of pheochromocytoma and hypertensive emergencies.
- Carvedilol is also used in the treatment of heart failure.
- Nebivolol is a **β1-selective blocker with vasodilating properties** that **are not mediated by α blockade**. The vasodilating effect may be due to an increase in endothelial release of nitric oxide via induction of endothelial nitric oxide synthase.

Mention the mechanism of action diuretics as antihypertensive.

Mention THREE side effects of loop diuretics

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.